# Dual biologic therapy in a patient with severe asthma and other allergic disorders

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## SUMMARY

Severe asthma is very difficult to manage in many individuals, and systemic corticosteroids are often used to prevent or manage acute exacerbations. Furthermore, comorbid allergic conditions may render standard therapies inadequate. A 51-year-old man presented with severe eosinophilic asthma requiring nearly constant oral corticosteroid usage despite using high-dose inhaled corticosteroids and secondary asthma controllers. His condition was complicated by aspirin-exacerbated respiratory disease, including severe nasal polyposis, chronic rhinosinusitis, as well as chronic idiopathic urticaria. Mepolizumab was initiated and led to dramatic improvement of asthma over 6 months. However, he continued to experience exacerbations of chronic idiopathic urticaria not responsive to H1-antihistamines. Omalizumab was added, and the patient's urticaria attained marked improvement with only an occasional breakthrough rash. Dual biologic therapies can be a unique and useful steroid-sparing treatment option for patients with uncontrolled severe asthma and chronic idiopathic urticaria.

## BACKGROUND

Severe persistent asthma is defined as asthma requiring high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled, or remaining uncontrolled despite treatment.[1 2] Phenotypic characterisation has helped classify this heterogenous group of patients into subgroups, with continuing research identifying pathways and targets for new therapies. Adult-onset severe asthma is more likely to present without atopy, with higher peripheral blood and sputum eosinophilia, and is associated with nasal obstruction and polyposis.[3] In addition, comorbid medical conditions complicate management of severe persistent asthma. Examples include aspirin sensitivity, gastro-oesophageal reflux and chronic rhinosinusitis.[4] Asthmatics also may have coexisting allergic disorders such as atopic dermatitis or chronic spontaneous urticaria (CSU). Multiple coexisting disorders further complicate treatment with conventional modalities and may contribute to the increased healthcare utilisation by those with severe persistent asthma.[4] Biologic therapies targeted against certain proinflammatory mediators have proven to be efficacious for asthma (interleukin-4 (IL-4) receptor, IL-5 and immunoglobulin E (IgE)) and other allergic conditions such as atopic dermatitis (IL-4 receptor) and CSU (IgE).[5–9] A specific biologic therapy is chosen based on history, laboratory evaluation, phenotype classification and associated comorbidities of severe persistent asthma. Herein is presented a unique case of a patient who has benefited from dual biologic therapy with mepolizumab and omalizumab to treat severe eosinophilic asthma complicated by aspirin-exacerbated respiratory disease (AERD), allergic rhinitis and CSU.

## CASE PRESENTATION

A 51-year-old male firefighter/paramedic presented to an allergy/asthma specialist with a 15-year history of wheezing, nightly cough causing nocturnal awakenings, nasal obstruction, anosmia and chronic hives. His history was significant for severe recurrent nasal polyposis requiring sinus surgeries 13 years, 9 years and 4 years prior. Worsening of nasal polyposis was associated with worsening of asthma. Notably, after the second procedure, he had a severe adverse reaction to ibuprofen characterised by acute dyspnoea, wheezing, urticaria, pruritus and angioedema. Home medications included mometasone/formoterol 200 µg/5 µg inhaler two puffs two times per day, montelukast 10 mg daily, cetirizine 10 mg daily, hydroxyzine 25–50 mg nightly, nebulised albuterol 2.5 mg up to every 4 hours and albuterol 90 µg rescue inhaler as needed. Additionally, he was taking triamcinolone 55 µg nasal spray two times per day. The patient brought medical records indicating previously performed skin tests indicating sensitisation to pet dander, trees, grasses and mould allergens. The patient did have a pet dog at home. He had been receiving subcutaneous immunotherapy injections for the previous 3 years without relief to allergic rhinitis symptoms.

Despite these treatments, the patient had uncontrolled daily symptoms and near-monthly exacerbations of wheezing, cough, dyspnoea, severe nasal congestion and postnasal drainage. He was being prescribed 30 mg oral prednisone on a 3-week tapered-dose schedule approximately 12 times per year from his primary physician or urgent care centre. He reported two additional emergency room visits but no hospitalisations for asthma exacerbations over the past 12 months. Furthermore, he suffered daily bouts of diffuse urticaria that did not respond to trials of cetirizine 40 mg daily and hydroxyzine 25 mg four times daily. Physical examination revealed diffuse urticaria, large bilateral nasal polyps and wheezing in all lung fields.

## INVESTIGATIONS

Prior to beginning biologic therapy, the patient consistently demonstrated airway obstruction with an forced expiratory volume in one second ($FEV_1$)

of 70% predicted and $FEV_1$/forced vital capacity (FVC) ratio of 50% predicted. At this time, the patient was still requiring chronic systemic corticosteroids to control his symptoms. Serum IgE was 236 kU/L. Allergy testing using allergen-specific serum IgE testing was negative to all allergens. An assay for urticaria-inducing autoantibodies was negative. Complete blood count showed absolute eosinophil count of 1150 cells/µL (normal value: <150 cells/µL). Fraction of exhaled nitric oxide (FENO) was 79 ppb (normal value: <25 ppb).

## TREATMENT

He was diagnosed with severe persistent uncontrolled asthma, eosinophilic phenotype. His secondary diagnoses were chronic rhinosinusitis with nasal polyposis (CRSwNP), AERD and CSU. Based on his chronic corticosteroid usage and exacerbation history, he was an excellent candidate for biologic therapy. He began mepolizumab 100 mg subcutaneous injection every 4 weeks. For the following 6 months, the patient reported significant reduction in symptoms of both asthma and CRSwNP without any uses or need for systemic corticosteroids. Despite the success, the patient still suffered from CSU resistant to high-dose H1-antihistamines. This urticaria was associated with severe pruritus, greatly affected sleep and reduced quality of daily living. He started omalizumab 300 mg subcutaneous injections every 4 weeks to specifically treat uncontrolled CSU. Given this patient's weight and serum IgE concentration, the dosage recommended for asthma control using omalizumab would have been 225 mg every 2 weeks. However, according to the most recent serum test, the patient lacked a positive perennial allergen sensitisation. Although omalizumab is also indicated for asthma, it is specifically indicated for atopic asthma, a different phenotype than eosinophilic asthma that this patient presented with. Thus, the decision to administer both biologics concurrently was medically appropriate and desirable to the patient.

## OUTCOME AND FOLLOW-UP

Since starting mepolizumab, the patient reported clearance of CRSwNP and resolution of asthma symptoms of dyspnoea, wheezing and nightly awakenings. Pulmonary function testing demonstrated improvement from an $FEV_1$ of 70% predicted to 112% predicted. $FEV_1$/FVC ratio increased from 50% to 86%. FENO reduced from 79 ppb at its peak to 15 ppb. As per guidelines, the patient has continued an asthma regimen of mometasone/formoterol 200 µg/5 µg inhaler two puffs two times per day, and montelukast 10 mg daily. He no longer required daily use of his nebulised albuterol, and he was able to discontinue daily intranasal steroid for CRSwNP. However, the patient's chronic urticaria remained resistant to treatment with H1-antihistamines and topical steroid cream. Omalizumab was added to the regimen approximately 6 months following initiation of mepolizumab to separately treat urticaria. Within 6 months, he had 90% improvement in his subjective urticaria symptoms. Breakthrough urticaria occurred occasionally over that time period but was much less diffuse and much more tolerable to the patient. Asthma symptoms remained well controlled, although there was no appreciable improvement in $FEV_1$ after addition of omalizumab (109% of predicted). He now requires only cetirizine 10 mg daily for symptoms of rhinitis and breakthrough urticaria. After nearly 4 years, the patient continues both mepolizumab and omalizumab with no adverse reactions. Currently, the patient no longer requires frequent high doses of corticosteroids courses to get through asthma and urticaria exacerbations. Subjectively, since beginning the combination biologic therapies, the patient reports great improvement in quality of life, sleep quality and removal of limitations on travel and exercise.

## DISCUSSION

The heterogeneity of severe persistent asthma and recent development of asthma phenotypes leads to a therapeutic challenge. Coexisting disorders further muddy the concept of simple phenotypes. In this patient, the presence of severe eosinophilic asthma, AERD and CSU caused uncontrolled symptoms for over a decade despite multiple standard asthma and allergy treatments. Until the approval of biologic agents, chronic systemic corticosteroid use was the final option for patients with persistent severe asthma, with resultant adverse effects such as skin atrophy, weight gain, hyperglycaemic, myopathy and osteoporosis. The patient in this case has benefitted from a personalised approach using two biologics targeting IL-5 and IgE.

Mepolizumab is an injectable monoclonal antibody that was approved in 2015 for adjuvant therapy in patients with severe asthma with eosinophilic phenotype.[10] Severe persistent asthma is characterised by the need for high-dose inhaled corticosteroids plus other add-on agents or requiring ≥2 rounds per year of systemic corticosteroids to control exacerbations, while the eosinophilic phenotype is characterised by the absolute eosinophil count of >150 cells/µL.[1 2] Both of these criteria were met by this patient on initial evaluation based on history and diagnostic evaluation. Mepolizumab works by target irreversibly binding IL-5, a cytokine responsible for eosinophil differentiation, maturation and survival. By blocking the signalling of IL-5, mepolizumab markedly reduces the number of eosinophils present in blood and sputum and reduces the frequency of exacerbations requiring systemic corticosteroids in eosinophilic asthma.[11 12] In addition to the eosinophilic phenotype, the patient has AERD, characterised by a triad of asthma, CRSwNP, and sensitivity to aspirin and non-steroidal anti-inflammatory drugs.[13] In 7.2% of all asthma patients, and in up to 14.9% of those with severe asthma, aspirin sensitivity can be present.[14] Even though mepolizumab is not approved specifically for its treatment, AERD may be associated with peripheral eosinophilia, and patients may demonstrate benefit from therapy with mepolizumab.[15] Aspirin desensitisation remains the definitive treatment for AERD in most patients; however, mepolizumab may serve as a bridge therapy for patients with severe persistent asthma and upper airway symptoms before attempting desensitisation.[15] For this individual, mepolizumab and exposure control remain the desired choice of treatment due to concern over the aspirin desensitisation procedure.

Despite success in controlling asthma exacerbations in this patient, the single therapy with mepolizumab did not adequately control symptoms related to CSU. Omalizumab is an injectable monoclonal antibody approved in 2003 that is indicated for moderate to severe persistent asthma with positive skin test, in vitro reactivity to a perennial aeroallergens, and is not controlled with inhaled corticosteroids.[16] In 2014, omalizumab was given an indication for treatment of CSU that is not controlled by H1-antihistamine treatment.[16] Its mechanism of action involves capturing IgE by binding to its Fc region, preventing binding to the high-affinity receptor (FcεRI) on mast cells and basophils.[17 18] Additionally,

omalizumab has been shown to remove IgE from the high-affinity receptor on these cells.[19] The reduced availability of IgE antibodies downregulates expression of the FcεRI receptor on mast cells and basophils, preventing degranulation.[17 18] Omalizumab administration was successful in reducing this patient's urticaria. He has been on both therapies for nearly 4 years.

Typically, addition of a specific biologic would be sufficient in managing refractory asthma. Because of this patient's comorbid and persistent CSU, a second biologic agent was needed until sufficient resolution of symptoms was achieved. This case demonstrates the heterogeneous and complex biology of severe persistent asthma that may not be completely understood. This combination of biologic therapies has not been studied extensively in severe persistent allergic and/or eosinophilic asthma. The use of these therapies to increase the quality of life and reduce the need for systemic corticosteroids and emergency care utilisation could provide benefit for severe eosinophilic asthma patients with concomitant AERD and CSU.

## Patient's perspective

Once I had been diagnosed with aspirin-exacerbated respiratory disease, the many years of severe asthma made much more sense. For a long time, I dealt with no sense of smell, terrible sleep quality and always waited on my next asthma exacerbation. I constantly relied on steroids to be able to breathe and to clear my congestion. The urticaria was another reason my quality of life suffered significantly. Since starting these two biologics, I am able to carry on with normal life again, travelling and exercising all the time without needing steroids to get to my next appointment.

## Learning points

- Severe persistent asthma may be complicated by comorbid allergic and non-allergic conditions such as chronic spontaneous urticaria and aspirin-exacerbated respiratory disease.
- Severe persistent asthma reduces quality of life and increases healthcare utilisation, especially when complicated by comorbid conditions.
- Combinations of biologic therapies may be safe and appropriate for severe persistent asthma and comorbid conditions.

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